Remarks

Reconsideration of this Application is respectfully requested.

Claims 1, 3-10, 13, and 25-50 are pending in the application, with claims 1, 8, 9, 10, 31, 38 and 44 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Priority

Applicants thank the Examiner for acknowledging that the Declaration by Dr. Bloch provides adequate proof that Applicants are entitled to their priority date for amended SEQ ID NO:3.

At the outset, Applicants would like to point out to the Examiner that claims 27, 28, 34, 35, 41, 42, 47 and 48 are related to nucleic acid molecules corresponding to SEQ ID NOS:3 and 4. SEQ ID NO:4 has not been amended in this application and the issue of priority for SEQ ID NO:4 has not been raised. The Examiner has acknowledged that the Declaration by Dr. Bloch substantiates that Applicants are entitled to their priority date for SEQ ID NO:3. Accordingly, Applicants request that the Examiner acknowledge that claims 27, 28, 34, 35, 41, 42, 47 and 48 are entitled to their priority dates.

With respect to SEQ ID NOS:1 and 2, the Examiner contends that there continues to be insufficient proof that amended SEQ ID NOS:1 and 2 are "one in the same" as those listed in the priority documents. Specifically, the Examiner asserted:

> the declaration signed by Dr. Li presents some ambiguity, see page 2 of declaration, paragraph 8. It is noted therein

> the deposited clones are *currently believed* to be the same as the coding sequence of currently amended SEQ ID NO:1 and SEQ ID NO:2. Essentially, it is not clear if SEQ ID NO:1 is the same as ATCC Deposit No. 2099933 and if SEQ ID NO:2 is the same as ATCC Deposit No. 209934. Applicants are required to make statements with unswerving clarity.

Office Action, at p. 2. The Examiner asserted that claims 1, 3-9, 13 and 25-50 continue to have the priority date of July 31, 2001. Applicants respectfully traverse this objection.

Applicants disagree with the Examiner that Dr. Li's statements are ambiguous and were not made with "unswerving clarity." Applicants requested that sequencing of the ATCC deposited clones (ATCC Deposit Nos. 209933 and 209934) corresponding to SEQ ID NOS:1 and 2 be performed to verify that the coding regions of amended SEQ ID NOS:1 and 2 are the same as the coding region of the ATCC Deposited clones. After reviewing the results, Dr. Li attested in the Declaration filed November 7, 2005, upon *information* and *belief*, that the coding sequences of the deposited clones are "currently believed to be the same" as the coding sequences of currently amended SEQ ID NO:1 and SEQ ID NO:2. *See* Paragraph Nos. 8 and 11 of the Declaration. Dr. Li's statement is clear and indicates that, upon information and belief, the coding sequences of the deposited clones are the same as the amended coding sequences. The Examiner appears to require the Declarant to make an *absolute* statement that the sequence is the same. While the Applicants do not wish to engage the Examiner in a scientific debate on whether absolute "truth" can even be attained, due to the inherent limits of perception and/or detection, Applicants respectfully submit that a statement made *on information and belief* is all that the law requires. Applicants further submit that such a statement has been made by Dr. Li in the Declaration filed November 7, 2005.

Applicants therefore believe, based on the above described Declaration by Dr. Li, that they are entitled to the June 25, 1998 filing date for sequences contained within ATCC Deposit Nos. 209933 and 209934. Accordingly, Applicants respectfully request that the Examiner acknowledge the Applicants' claim to priority.

Objections to the Specification

On page 5 of the Office Action, the Examiner maintains the objection to Figures 1A1 to 1A-4, 1B-1 to 1B-4, 2A, 2B, 3A-1 and 3A-2 under 35 U.S.C. § 132 as allegedly introducing new matter into the disclosure. The Examiner objected that the polynucleotides shown in the Figures do not have adequate support in the priority documents by reference to the deposits.

As described above under "***Priority***," the polynucleotides shown in the amended Figures have adequate support in the priority documents by reference to the ATCC deposits. Thus, no new matter was added to the disclosure by submission of the corrected Figures. Accordingly, Applicants respectfully request that the Examiner withdraw the objection.

Rejections Under 35 U.S.C. § 112, First Paragraph (enablement)

On pages 5-7 of the Office Action, the Examiner maintained the rejection to claims 1, 3-10, 13 and 25-50 under 35 U.S.C. §112, first paragraph, allegedly because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The Examiner contends Applicants' specification does not provide adequate guidance and does not provide adequate information enabling the

making and using of variant molecules and a single polynucleotide sequence as listed in claims 1(f), 8(b), 9(b) and 10(b). The Examiner further asserted that the specification does not provide guidance for implementing the method of claim 13 with a mutant polypeptide encoded by a nucleic acid of claim 1, in particular those of sections (e) and (f) of claim 1. The Examiner further alleged that given the insufficient guidance, the changes which must be made in the nucleic acid sequences of SEQ ID NO:1-4, which results in nucleic acid sequences with 90% identity and the implementation of one polynucleotide sequence is unpredictable and the experimentation left to those skilled in the art is unnecessary and improperly extensive and undue. Applicants respectfully traverse this rejection.

Applicants would like to first point out that claims 25-28 are directed to polynucleotides encoding polypeptides corresponding to SEQ ID NOS:5-8, claims 32-35 are directed to nucleic acid molecules contained in ATCC deposits, and claims 45-48 are directed to specific SEQ ID NOS. Thus, Applicants are unclear why the Examiner has rejected these claims for lack of enablement.

While Applicants thank the Examiner for withdrawing the second enablement rejection, Applicants would like to also respectfully point out that the Examiner has taken some contradictory positions regarding enablement of the claimed invention during prosecution. Applicants submit that these contradictory positions have hurt Applicants' attempts to advance the prosecution of the application. For instance, in the Office Action dated March 10, 2004, the Examiner admitted that "the making of the claimed polynucleotides may not be burdensome" but argued that "the claims do not limit which particular functions they should or should not be able to perform." *Office*

Action, dated March 10, 2004. Based on the Examiner's statements, Applicants understood the Examiner's rejection of the claims as not pertaining to the making of the polynucleotide, but rather to the use thereof because there was no functional limitation on which particular functions the nucleic acid molecule performs. In the Applicants' Amendment and Reply filed on March 10, 2005, Applicants amended the claims to recite a specific function performed by the polynucleotide, *viz.*, the function of encoding a polypeptide capable of methylating DNA in an *in vitro* assay. Therefore, Applicants believed that the claim amendments made on March 10, 2005 addressed the Examiner's enablement rejection. In the following Office Action, the Examiner issued two enablement rejections, both of which appeared to not take into consideration the Applicants' amendment adding functional limitations to the claims. In the first enablement rejection the Examiner made the following comments:

> [t]he 90% sequence identical polynucleotides may encode polypeptides that may not maintain the activities proposed in the specification. . . . It would seem that specific function(s) would be required to make the encoded protein useful for the applications disclosed in the specification, such as *in vitro* methylation at the C5 position of cytosine in DNA.

Office Action of June 6, 2005, pages 4-5. In a second enablement rejection in the same Office Action, the Examiner again admitted that the making of the mutants would not be undue but that the claims lacked functional limitations:

> Applicants have not supplied information relative to the use of these claimed mutants. While the making of the claimed polynucleotides may not be burdensome implementing these variants in the proposed applications of the specification may not be valid. . . . The claims do not limit which particular functions the mutants should exhibit or preclude what functions they should or should not be able to perform.

Id. at p. 7. In the reply filed November 7, 2005, Applicants pointed out that the claims had been previously amended to specify the particular function the polynucleotides should perform, *viz.*, the polynucleotides encoded polypeptides capable of methylating DNA. *Amendment and Reply* of November 7, 2005, p. 19. The Applicants pointed out that claims 8, 9 and 10 were now limited to polynucleotide probes or primers. *Id.* at p. 20. Now, in spite of the Examiner's previous assertions that the making of the claimed polynucleotides are not undue, the Examiner has reversed course and takes the position that the making of the claimed polynucleotides is undue.

> The making of the claimed polynucleotides may not be burdensome given one of ordinary skill in the art is given adequate information such as which residues should residues should be mutate [sic], deleted, substituted or unchanged. The amount of experimentation required to undertake such tasks would be length and problematic.

Office Action, page 6.

In any event, Applicants submit that the pending claims are enabled and respectfully refer the Examiner to the "Training Materials for Examining Patent Applications with Respect To 35 U.S.C. 112, First Paragraph - Enablement Chemical/Biotechnical Applications." ("the Training Materials"). Specifically, the enablement decision tree set forth in the Training Materials first asks the question: "Does the specification teach how to make and use at least one embodiment encompassed by the claims as a whole without undue experimentation?" A note to the question states: "if there is a working example, the answer to the question cannot be 'NO'." The Applicants not only provide general guidance as to how to make and use embodiments of the claimed invention but also describe representative species that fall

within the scope of the claimed invention (*i.e.*, polynucleotides encoded by SEQ ID NOS:1-4). Accordingly, the answer to the first question is necessarily "yes."

The second question in the enablement decision tree is: "Are the enabled embodiments representative of the full scope of the claim?" Under the Training Materials for the written description requirement, the USPTO has deemed that a single disclosed species is representative of a claimed genus of DNA hybridizing homologs and sequence variants encompassed by the claims.[1] Specifically, the high degree of sequence identity required by the claims yields structurally similar nucleotides; therefore, a person of skill in the art would not expect substantial variation among species within the genus. Accordingly, as Applicants have disclosed at least one representative species (*i.e.*, SEQ ID NOS:1-4), the answer to this second question is necessarily "yes." Thus, Applicants submit that following the guidelines of the enablement decision tree, no enablement rejection should be made under these circumstances.

Applicants believe that, in view of the high degree of sequence identity required by the claims, one skilled in the art would readily understand that the proteins encoded by the claimed nucleic acid molecule have strong probability to exhibit the same

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[1] See http://www.uspto.gov/web/menu/written.pdf). Specifically, the Examiner's attention is directed to Example 14 of the Training Materials, which analyzes a claim directed to variants of a protein that are at least 95% identical to a particular disclosed sequence and that have a particularly specified activity. Therein, the PTO concludes that "the genus of proteins that must be variants . . . *does not have substantial variation* since all the variants must possess the specific catalytic activity and must have at least 95% identity to the reference sequence." Thus, "the single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provides for identifying all of the at least 95% identical variants . . . which are capable of the specified catalytic activity." Accordingly, "one skilled in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus" (*i.e.*, the example claim meets the written description requirement of 35 U.S.C. §112, first paragraph). *See* pages 53-55 of the Training Materials.

function as the reference sequences (*i.e.*, SEQ ID NOS:1-4). Furthermore, independent claims 1, 31, 38 and 44 specify that the proteins encoded by the claimed nucleic acids possess a specific enzymatic function, namely that the encoded polypeptide is capable of methylating DNA in an *in vitro* assay. The Applicants specification provides ample direction as to how one skilled in the art can assess the capability of such variants to perform the specified function. Specifically, Example 4 of the specification sets forth how to assay methyltransferase activity. As such, Applicants believe one of ordinary skill in the art would be able to make and use the nucleic acid molecules of the claims without undue experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph (written description)

The Examiner rejected claim 10 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *See Office Action* at p. 7. Applicants respectfully traverse the written description rejection.

The Examiner contends that the Applicants' specification is remiss of sufficient information, guidance and sincere contemplation of an oligonucleotide probe or primer of at least 100 contiguous nucleotides in length. The Examiner has relied on *In re Ruschig* for the proposition that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species.

The genus disclosed on page 21, lines 17-25 of the specification discloses the range of fragment sizes by a mathematical formula. The Examiner appears to require that the Applicants' claimed subgenus be described in *ipsis verbis*. Applicants assert that there is no such requirement in the patent law. Applicants respectfully point out that they are fully within their rights to represent their invention by formula, as the law clearly establishes that one may show that one is in possession of the invention by describing the invention, with all its claimed limitations by such descriptive means as "words, structures, figures, diagrams, *formulas*, etc., that fully set forth the claimed invention." *See Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis added). Applicants assert that a person of ordinary skill in the art would envision each and every fragment size because the fragment size is the only variable and the formula teaches each and every fragment size. Moreover, a person of ordinary skill in the art would understand that Applicants were in possession of each fragment size.

In addition, Applicants note that courts have stressed that the precedential value of cases in this area are extremely limited and that each case must be decided on its own facts. *In re Driscoll*, 562 F.2d 1245, 1250 (CCPA 1977). Nonetheless, Applicants have argued, and maintain that *In re Ruschig* is not the most relevant precedent because the *Ruschig* court held that disclosure of a *genus* of compounds indicated by a chemical formula does not disclose an individual *species* where there are *several independent variables* to choose from to arrive at the individual species and the specification lacks such guidance to reasonably lead the skilled artisan to the species. In contrast, claim 10 is drawn to a *subgenus*, not a species, and requires selection of only one variable to

arrive at the claimed subgenus, *viz.*, the size of the fragment. While the written description cases dealing with genus-species and genus-subgenus relationships are grounded on similar principles, Applicants submit that the more relevant cases vis-à-vis claim 10 are those that address whether the disclosure of a genus provides adequate support for a subgenus.

Fujikawa v. Wattanasin, 93 F.3d 1559 (Fed. Cir. 1996) is such a case. *Fujikawa* held that disclosure of a broad genus disclosing various possible substituents at *several variable* positions did not disclose a subgenus where the moiety was limited to a single substituent at two of the positions. The court noted that the disclosure provided no indication that the position would be a better candidate for substitution than any other. In contrast, where the whole focus of the specification is on substituents at a *single* position, the court in *Driscoll* held that disclosure of a genus having five variable groups disclosed a subgenus where one of the groups was limited at a single position which was highlighted by the specification. 562 F.2d at 1249-1250. Thus, the courts have held that a genus disclosing several variable groups will disclose a subgenus in cases where a single group was limited, as long as the specification highlighted that single group.

As noted above, the crux of the Examiner's position is the proposition that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. The Applicants do not disagree with the Examiner's proposition as it may be applied to cases like *Fujikawa* and *Ruschig*, which required the artisan to make *several*, *independent* selections of Markush group members from the genus to arrive at the claimed subgenus or species, and the specification did not

provide any guidance as to which *combinations* of selections were to be made. Applicants seriously doubt, however, that these cases or the Examiner's proposition, extend to situations where, as here, the artisan is required to select from only *one* variable of a genus to arrive at the claimed subgenus. Because selection of only one variable is required here, the Applicants submit that the specification reasonably leads the artisan to each and every fragment size described by the formula and thus the skilled artisan would comprehend that the formula discloses fragments of at least 100 contiguous nucleotides of SEQ ID NO:3.

Based on the forgoing, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection of claim 10 under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 102

First, the Examiner rejected claims 1, 3-9, and 25-50 under 35 U.S.C. § 102(b) as allegedly anticipated by Okano *et al.* as evidenced by Accession numbers AF068625, AF068626 and AF068627. See Office Action at p. 7-8. Second, the Examiner rejected claims 1, 3-9, 25-50 under 35 U.S.C. 102(b) as allegedly anticipated by Xie *et al.* as evidenced by Accession number AF067972. *Id.* at p. 8. Applicants traverse these rejections as they may be applied to the pending claims.

Applicants again object to the Examiner's rejection of claim 28, 35, 42 and 48 which relate to isolated nucleic acid molecules encoding SEQ ID NO:4. Applicants point out to the Examiner that the polynucleotide encoding SEQ ID NO:4 is disclosed in the priority application and has not been amended. Thus, it cannot be disputed that SEQ

ID NO:4 is supported by the priority application. In addition, Applicants object to the Examiner's rejection of claims 27, 34, 41 and 47, which relate to isolated nucleic acid molecules encoding SEQ ID NO:3. The Examiner has acknowledged that SEQ ID NO:3 is supported by the priority application.

Applicants submit that the Declaration by Dr. En Li substantiates that, as currently believed, the coding regions of the cDNA sequences contained within ATCC Deposit Nos. 209933 and 209934 are the same as the coding regions of currently amended SEQ ID NOS:1-2, respectively.

Accordingly, Applicants respectfully submit that Okano *et al.* and Xie *et al.* are not prior art and therefore respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1, 3-9, 13, 25-50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Okano *et al.*, as evidenced by Accession number AF068625, AF068626 and AF068627 and in view of U.S. Patent No. 6,492,168 B1 ("the '168 patent"). The Examiner also rejected claims 1, 3-9, 13, and 25-50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Xie *et al.*, as evidenced by Accession number AF067972, and in view of the '168 patent. *Id.* Applicants respectfully traverse this rejection.

Applicants object to the Examiner's rejection of claims 27, 28, 34, 35, 41, 42, 47 and 48 for the reasons stated above under "***Rejections Under 35 U.S.C. § 102***."

Applicants submit that the Declaration by Dr. En Li substantiates that, as currently believed, the coding regions of the cDNA sequences contained within ATCC Deposit Nos. 209933 and 209934 are the same as the coding regions of currently amended SEQ ID NOS:1-2, respectively.

Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

Double Patenting Rejection

On page 9 of the Office Action, the Examiner provisionally rejected claims 1, 3-10, 13, and 25-50 under 35 U.S.C. § 101 as claiming the same invention as that of claims 51-55 of copending Application No. 10/623,813. Applicants respectfully traverse this rejection.

Applicants respectfully assert that claims 1, 3-10, 13 and 25-50 are not directed to the same invention of claims 51-55 of copending Application No. 10/623,813. A rejection based on the statutory type of double patenting is improper if the claims are not coextensive in scope. Claims 51-55 are directed to polynucleotide sequences contained in ATCC Deposit Nos. PTA-4611 and PTA-4610. The deposited polynucleotides relate to mouse and human Dnmt3a2, which are short isoforms of mouse and human Dnmt3a. The Dnmt3a2 sequences differ from the Dnmt3a sequences in that they are shorter isoforms. Thus, claims 51-55 are not coextensive in scope with claims 1, 3-10, 13 and 25-50.

Accordingly, Applicants respectfully request that the provisional double patenting rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned directly at (202)772-8637.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Karen R. Markowicz

Karen R. Markowicz
Agent for Applicants
Registration No. 36,351

Date: 6/23/06

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600